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(54) Title: METHOD OF DIAGNOSING, MONITORING, STAGING, IMAGING AND TREATING PROSTATE CANCER

(57) Abstract

The present invention provides new methods for detecting, diagnosing, monitoring, staging, prognosticating, imaging and treating prostate cancer.

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METHOD OF DIAGNOSING, MONITORING, STAGING, IMAGING AND TREATING PROSTATE CANCER

FIELD OF THE INVENTION

This invention relates, in part, to newly developed assays for detecting, diagnosing, monitoring, staging, prognosticating, imaging and treating cancers, particularly prostate cancer.

BACKGROUND OF THE INVENTION

Cancer of the prostate is the most prevalent malignancy in adult males, excluding skin cancer, and is an increasingly prevalent health problem in the United States. In 1996, it was estimated that 41,400 deaths would result from this disease in the United States alone, indicating that prostate cancer is second only to lung cancer as the most common cause of death in the same population. If diagnosed and treated early, when the cancer is still confined to the prostate, the chances of cure is significantly higher.

Treatment decisions for an individual are linked to the stage of prostate cancer present in that individual. A common classification of the spread of prostate cancer was developed by the American Urological Association (AUA). The AUA system divides prostate tumors into four stages, A to D. Stage A, microscopic cancer within prostate, is further subdivided into stages A1 and A2. Sub-stage A1 is a well-differentiated cancer confined to one site within the prostate. Treatment is generally observation, radical prostatectomy, or radiation. Sub-stage A2 is a moderately to poorly differentiated cancer at multiple sites within the prostate. Treatment is radical prostatectomy or radiation. Stage B, palpable lump within the prostate, is also further subdivided into sub-stages B1 and B2. In sub-stage B1, the cancer forms a small nodule in one

lobe of the prostate. In sub-stage B2, the cancer forms large or multiple nodules, or occurs in both lobes of the prostate. Treatment for sub-stages B1 and B2 is either radical prostatectomy or radiation. Stage C is a large cancer mass involving most or all of the prostate and is also further subdivided into two sub-stages. In sub-stage C1, the cancer forms a continuous mass that may have extended beyond the prostate. In sub-stage C2, the cancer forms a continuous mass that invades the surrounding tissue. Treatment for both these sub-stages is radiation with or without drugs to address the cancer. The fourth stage, Stage D is metastatic cancer and is also subdivided into two sub-stages. In sub-stage D1, the cancer appears in the lymph nodes of the pelvis. In sub-stage D2, the cancer involves tissues beyond lymph nodes. Treatment for both of these sub-stages is systemic drugs to address the cancer as well as pain.

However, current prostate cancer staging methods are limited. As many as 50% of prostate cancers initially staged as A2, B, or C are actually stage D, metastatic. Discovery of metastasis is significant because patients with metastatic cancers have a poorer prognosis and require significantly different therapy than those with localized cancers. The five year survival rates for patients with localized and metastatic prostate cancers are 93% and 29%, respectively.

Accordingly, there is a great need for more sensitive and accurate methods for the staging of a cancer in a human to determine whether or not such cancer has metastasized and for monitoring the progress of a cancer in a human which has not metastasized for the onset of metastasis.

It has now been found that a number of proteins in the public domain are useful as diagnostic markers for prostate cancer. These diagnostic markers are referred to herein as cancer specific genes or CSGs and include, but are not limited to: Pro109 which is a human zinc-α 2-glycoprotein (Freje et al. Genomics 1993 18(3):575-587); Pro112 which is a human

cysteine-rich protein with a zinc-finger motif (Liebhaber et al. Nucleic Acid Research 1990 18(13):3871-3879; WO9514772 and WO9845436); Pro111 which is a prostate-specific transglutaminase (Dubbink et al. Genomics 1998 51(3):434-444); Pro115 which is a novel serine protease with transmembrane, LDLR, and SRCR domains and maps to 21q22.3 (Paoloni-Giacobino et al. Genomics 1997 44(3):309-320; WO9837418 and WO987093); Pro110 which is a human breast carcinoma fatty acid synthase (U.S. Patent 5,665,874 and WO9403599); Pro113 which is a homeobox gene, HOXB13 (Steinicki et al. J. Invest. Dermatol. 1998 111:57-63); Pro114 which is a human tetraspan NET-1 (WO9839446); and Pro118 which is a human JM27 protein (WO9845435). ESTs for these CSGs are set forth in SEQ ID NO: 1, 3, 5, 7, 9, 11, 13 and 15 while the full length contigs for these CSGs are set forth in SEQ ID NO:2, 4, 6, 8, 10, 12, 14 and 16, respectively. Additional CSGs for use in the present invention are depicted herein in SEQ ID NO: 17, 18, 19 and 20.

In the present invention, methods are provided for detecting, diagnosing, monitoring, staging, prognosticating, imaging and treating prostate cancer via the cancer specific genes referred to herein as CSGs. For purposes of the present invention, CSG refers, among other things, to native protein expressed by the gene comprising a polynucleotide sequence of SEQ ID NO:1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20. By "CSG" it is also meant herein polynucleotides which, due to degeneracy in genetic coding, comprise variations in nucleotide sequence as compared to SEQ ID NO: 1-20, but which still encode the same protein. In the alternative, what is meant by CSG as used herein, means the native mRNA encoded by the gene comprising the polynucleotide sequence of SEQ ID NO:1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20, levels of the gene comprising the polynucleotide sequence of SEQ ID NO:1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20, or levels of a polynucleotide which is capable of

hybridizing under stringent conditions to the antisense sequence of SEQ ID NO:1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20.

Other objects, features, advantages and aspects of the present invention will become apparent to those of skill in the art from the following description. It should be understood, however, that the following description and the specific examples, while indicating preferred embodiments of the invention are given by way of illustration only. Various changes and modifications within the spirit and scope of the disclosed invention will become readily apparent to those skilled in the art from reading the following description and from reading the other parts of the present disclosure.

SUMMARY OF THE INVENTION

Toward these ends, and others, it is an object of the present invention to provide a method for diagnosing the presence of prostate cancer by analyzing for changes in levels of CSG in cells, tissues or bodily fluids compared with levels of CSG in preferably the same cells, tissues, or bodily fluid type of a normal human control, wherein a change in levels of CSG in the patient versus the normal human control is associated with prostate cancer.

Further provided is a method of diagnosing metastatic prostate cancer in a patient having prostate cancer which is not known to have metastasized by identifying a human patient suspected of having prostate cancer that has metastasized; analyzing a sample of cells, tissues, or bodily fluid from such patient for CSG; comparing the CSG levels in such cells, tissues, or bodily fluid with levels of CSG in preferably the same cells, tissues, or bodily fluid type of a normal human control, wherein an increase in CSG levels in the patient versus the normal human control is associated with prostate cancer which has metastasized.

Also provided by the invention is a method of staging prostate cancer in a human which has such cancer by identifying a human patient having such cancer; analyzing a sample of cells, tissues, or bodily fluid from such patient for CSG; comparing CSG levels in such cells, tissues, or bodily fluid with levels of CSG in preferably the same cells, tissues, or bodily fluid type of a normal human control sample, wherein an increase in CSG levels in the patient versus the normal human control is associated with a cancer which is progressing and a decrease in the levels of CSG is associated with a cancer which is regressing or in remission.

Further provided is a method of monitoring prostate cancer in a human having such cancer for the onset of metastasis. The method comprises identifying a human patient having such cancer that is not known to have metastasized; periodically analyzing a sample of cells, tissues, or bodily fluid from such patient for CSG; comparing the CSG levels in such cells, tissue, or bodily fluid with levels of CSG in preferably the same cells, tissues, or bodily fluid type of a normal human control sample, wherein an increase in CSG levels in the patient versus the normal human control is associated with a cancer which has metastasized.

Further provided is a method of monitoring the change in stage of prostate cancer in a human having such cancer by looking at levels of CSG in a human having such cancer. The method comprises identifying a human patient having such cancer; periodically analyzing a sample of cells, tissues, or bodily fluid from such patient for CSG; comparing the CSG levels in such cells, tissue, or bodily fluid with levels of CSG in preferably the same cells, tissues, or bodily fluid type of a normal human control sample, wherein an increase in CSG levels in the patient versus the normal human control is associated with a cancer which is progressing and a decrease in the levels of CSG is associated with a cancer which is regressing or in remission.

Further provided are methods of designing new therapeutic agents targeted to a CSG for use in imaging and treating prostate cancer. For example, in one embodiment, therapeutic agents such as antibodies targeted against CSG or fragments of such antibodies can be used to detect or image localization of CSG in a patient for the purpose of detecting or diagnosing a disease or condition. Such antibodies can be polyclonal, monoclonal, or omniclonal or prepared by molecular biology techniques. The term "antibody", as used herein and throughout the instant specification is also meant to include aptamers and single-stranded oligonucleotides such as those derived from an *in vitro* evolution protocol referred to as SELEX and well known to those skilled in the art. Antibodies can be labeled with a variety of detectable labels including, but not limited to, radioisotopes and paramagnetic metals. Therapeutics agents such as antibodies or fragments thereof can also be used in the treatment of diseases characterized by expression of CSG. In these applications, the antibody can be used without or with derivatization to a cytotoxic agent such as a radioisotope, enzyme, toxin, drug or a prodrug.

Other objects, features, advantages and aspects of the present invention will become apparent to those of skill in the art from the following description. It should be understood, however, that the following description and the specific examples, while indicating preferred embodiments of the invention, are given by way of illustration only. Various changes and modifications within the spirit and scope of the disclosed invention will become readily apparent to those skilled in the art from reading the following description and from reading the other parts of the present disclosure.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to diagnostic assays and methods, both quantitative and qualitative for detecting, diagnosing, monitoring, staging and prognosticating cancers

by comparing levels of CSG in a human patient with those of CSG in a normal human control. For purposes of the present invention, what is meant be CSG levels is, among other things, native protein expressed by the gene comprising a polynucleotide sequence of SEQ ID NO:1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20. By "CSG" it is also meant herein polynucleotides which, due to degeneracy in genetic coding, comprise variations in nucleotide sequence as compared to SEQ ID NO: 1-20, but which still encode the same protein. The native protein being detected, may be whole, a breakdown product, a complex of molecules or chemically modified. In the alternative, what is meant by CSG as used herein, means the native mRNA encoded by the gene comprising the polynucleotide sequence of SEQ ID NO:1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20, levels of the gene comprising the polynucleotide sequence of SEQ ID NO:1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20, or levels of a polynucleotide which is capable of hybridizing under stringent conditions to the antisense sequence of SEQ ID NO:1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20. Such levels are preferably determined in at least one of, cells, tissues and/or bodily fluids, including determination of normal and abnormal levels. Thus, for instance, a diagnostic assay in accordance with the invention for diagnosing overexpression of CSG protein compared to normal control bodily fluids, cells, or tissue samples may be used to diagnose the presence of prostate cancer.

All the methods of the present invention may optionally include determining the levels of other cancer markers as well as CSG. Other cancer markers, in addition to CSG, useful in the present invention will depend on the cancer being tested and are known to those of skill in the art.

Diagnostic Assays

The present invention provides methods for diagnosing the presence of prostate cancer by analyzing for changes in levels of CSG in cells, tissues or bodily fluids compared with levels of CSG in cells, tissues or bodily fluids of preferably the same type from a normal human control, wherein an increase in levels of CSG in the patient versus the normal human control is associated with the presence of prostate cancer.

Without limiting the instant invention, typically, for a quantitative diagnostic assay a positive result indicating the patient being tested has cancer is one in which cells, tissues or bodily fluid levels of the cancer marker, such as CSG, are at least two times higher, and most preferably are at least five times higher, than in preferably the same cells, tissues or bodily fluid of a normal human control.

The present invention also provides a method of diagnosing metastatic prostate cancer in a patient having prostate cancer which has not yet metastasized for the onset of metastasis. In the method of the present invention, a human cancer patient suspected of having prostate cancer which may have metastasized (but which was not previously known to have metastasized) is identified. This is accomplished by a variety of means known to those of skill in the art.

In the present invention, determining the presence of CSG levels in cells, tissues or bodily fluid, is particularly useful for discriminating between prostate cancer which has not metastasized and prostate cancer which has metastasized. Existing techniques have difficulty discriminating between prostate cancer which has metastasized and prostate cancer which has not metastasized and proper treatment selection is often dependent upon such knowledge.

In the present invention, the cancer marker levels measured in such cells, tissues or bodily fluid is CSG, and are compared with levels of CSG in preferably the same cells, tissue or bodily fluid type of a normal human control. That

is, if the cancer marker being observed is just CSG in serum, this level is preferably compared with the level of CSG in serum of a normal human control. An increase in the CSG in the patient versus the normal human control is associated with prostate cancer which has metastasized.

Without limiting the instant invention, typically, for a quantitative diagnostic assay a positive result indicating the cancer in the patient being tested or monitored has metastasized is one in which cells, tissues or bodily fluid levels of the cancer marker, such as CSG, are at least two times higher, and most preferably are at least five times higher, than in preferably the same cells, tissues or bodily fluid of a normal patient.

Normal human control as used herein includes a human patient without cancer and/or non cancerous samples from the patient; in the methods for diagnosing or monitoring for metastasis, normal human control may preferably also include samples from a human patient that is determined by reliable methods to have prostate cancer which has not metastasized.

Staging

The invention also provides a method of staging prostate cancer in a human patient. The method comprises identifying a human patient having such cancer and analyzing cells, tissues or bodily fluid from such human patient for CSG. The CSG levels determined in the patient are then compared with levels of CSG in preferably the same cells, tissues or bodily fluid type of a normal human control, wherein an increase in CSG levels in the human patient versus the normal human control is associated with a cancer which is progressing and a decrease in the levels of CSG (but still increased over true normal levels) is associated with a cancer which is regressing or in remission.

Monitoring

Further provided is a method of monitoring prostate cancer in a human patient having such cancer for the onset of

metastasis. The method comprises identifying a human patient having such cancer that is not known to have metastasized; periodically analyzing cells, tissues or bodily fluid from such human patient for CSG; and comparing the CSG levels determined in the human patient with levels of CSG in preferably the same cells, tissues or bodily fluid type of a normal human control, wherein an increase in CSG levels in the human patient versus the normal human control is associated with a cancer which has metastasized. In this method, normal human control samples may also include prior patient samples.

Further provided by this invention is a method of monitoring the change in stage of prostate cancer in a human patient having such cancer. The method comprises identifying a human patient having such cancer; periodically analyzing cells, tissues or bodily fluid from such human patient for CSG; and comparing the CSG levels determined in the human patient with levels of CSG in preferably the same cells, tissues or bodily fluid type of a normal human control, wherein an increase in CSG levels in the human patient versus the normal human control is associated with a cancer which is progressing in stage and a decrease in the levels of CSG is associated with a cancer which is regressing in stage or in remission. In this method, normal human control samples may also include prior patient samples.

Monitoring a patient for onset of metastasis is periodic and preferably done on a quarterly basis. However, this may be more or less frequent depending on the cancer, the particular patient, and the stage of the cancer.

Assay Techniques

Assay techniques that can be used to determine levels of gene expression (including protein levels), such as CSG of the present invention, in a sample derived from a patient are well known to those of skill in the art. Such assay methods include, without limitation, radioimmunoassays, reverse transcriptase PCR (RT-PCR) assays, immunohistochemistry

assays, *in situ* hybridization assays, competitive-binding assays, Western Blot analyses, ELISA assays and proteomic approaches: two-dimensional gel electrophoresis (2D electrophoresis) and non-gel based approaches such as mass spectrometry or protein interaction profiling. Among these, ELISAs are frequently preferred to diagnose a gene's expressed protein in biological fluids.

An ELISA assay initially comprises preparing an antibody, if not readily available from a commercial source, specific to CSG, preferably a monoclonal antibody. In addition a reporter antibody generally is prepared which binds specifically to CSG. The reporter antibody is attached to a detectable reagent such as radioactive, fluorescent or enzymatic reagent, for example horseradish peroxidase enzyme or alkaline phosphatase.

To carry out the ELISA, antibody specific to CSG is incubated on a solid support, e.g. a polystyrene dish, that binds the antibody. Any free protein binding sites on the dish are then covered by incubating with a non-specific protein such as bovine serum albumin. Next, the sample to be analyzed is incubated in the dish, during which time CSG binds to the specific antibody attached to the polystyrene dish. Unbound sample is washed out with buffer. A reporter antibody specifically directed to CSG and linked to a detectable reagent such as horseradish peroxidase is placed in the dish resulting in binding of the reporter antibody to any monoclonal antibody bound to CSG. Unattached reporter antibody is then washed out. Reagents for peroxidase activity, including a colorimetric substrate are then added to the dish. Immobilized peroxidase, linked to CSG antibodies, produces a colored reaction product. The amount of color developed in a given time period is proportional to the amount of CSG protein present in the sample. Quantitative results typically are obtained by reference to a standard curve.

A competition assay can also be employed wherein antibodies specific to CSG are attached to a solid support and labeled CSG and a sample derived from the host are passed over the solid support. The amount of label detected which is attached to the solid support can be correlated to a quantity of CSG in the sample.

Nucleic acid methods can also be used to detect CSG mRNA as a marker for prostate cancer. Polymerase chain reaction (PCR) and other nucleic acid methods, such as ligase chain reaction (LCR) and nucleic acid sequence based amplification (NASABA), can be used to detect malignant cells for diagnosis and monitoring of various malignancies. For example, reverse-transcriptase PCR (RT-PCR) is a powerful technique which can be used to detect the presence of a specific mRNA population in a complex mixture of thousands of other mRNA species. In RT-PCR, an mRNA species is first reverse transcribed to complementary DNA (cDNA) with use of the enzyme reverse transcriptase; the cDNA is then amplified as in a standard PCR reaction. RT-PCR can thus reveal by amplification the presence of a single species of mRNA. Accordingly, if the mRNA is highly specific for the cell that produces it, RT-PCR can be used to identify the presence of a specific type of cell.

Hybridization to clones or oligonucleotides arrayed on a solid support (*i.e.* gridding) can be used to both detect the expression of and quantitate the level of expression of that gene. In this approach, a cDNA encoding the CSG gene is fixed to a substrate. The substrate may be of any suitable type including but not limited to glass, nitrocellulose, nylon or plastic. At least a portion of the DNA encoding the CSG gene is attached to the substrate and then incubated with the analyte, which may be RNA or a complementary DNA (cDNA) copy of the RNA, isolated from the tissue of interest. Hybridization between the substrate bound DNA and the analyte can be detected and quantitated by several means including but

not limited to radioactive labeling or fluorescence labeling of the analyte or a secondary molecule designed to detect the hybrid. Quantitation of the level of gene expression can be done by comparison of the intensity of the signal from the analyte compared with that determined from known standards. The standards can be obtained by *in vitro* transcription of the target gene, quantitating the yield, and then using that material to generate a standard curve.

Of the proteomic approaches, 2D electrophoresis is a technique well known to those in the art. Isolation of individual proteins from a sample such as serum is accomplished using sequential separation of proteins by different characteristics usually on polyacrylamide gels. First, proteins are separated by size using an electric current. The current acts uniformly on all proteins, so smaller proteins move farther on the gel than larger proteins. The second dimension applies a current perpendicular to the first and separates proteins not on the basis of size but on the specific electric charge carried by each protein. Since no two proteins with different sequences are identical on the basis of both size and charge, the result of a 2D separation is a square gel in which each protein occupies a unique spot. Analysis of the spots with chemical or antibody probes, or subsequent protein microsequencing can reveal the relative abundance of a given protein and the identity of the proteins in the sample.

The above tests can be carried out on samples derived from a variety of cells, bodily fluids and/or tissue extracts such as homogenates or solubilized tissue obtained from a patient. Tissue extracts are obtained routinely from tissue biopsy and autopsy material. Bodily fluids useful in the present invention include blood, urine, saliva or any other bodily secretion or derivative thereof. By blood it is meant to include whole blood, plasma, serum or any derivative of blood.

In Vivo Targeting of CSGs

Identification of these CSGs is also useful in the rational design of new therapeutics for imaging and treating cancers, and in particular prostate cancer. For example, in one embodiment, antibodies which specifically bind to CSG can be raised and used *in vivo* in patients suspected of suffering from prostate cancer. Antibodies which specifically bind a CSG can be injected into a patient suspected of having prostate cancer for diagnostic and/or therapeutic purposes. The preparation and use of antibodies for *in vivo* diagnosis is well known in the art. For example, antibody-chelators labeled with Indium-111 have been described for use in the radioimmunoscintographic imaging of carcinoembryonic antigen expressing tumors (Sumerdon et al. Nucl. Med. Biol. 1990 17:247-254). In particular, these antibody-chelators have been used in detecting tumors in patients suspected of having recurrent colorectal cancer (Griffin et al. J. Clin. Onc. 1991 9:631-640). Antibodies with paramagnetic ions as labels for use in magnetic resonance imaging have also been described (Lauffer, R.B. Magnetic Resonance in Medicine 1991 22:339-342). Antibodies directed against CSG can be used in a similar manner. Labeled antibodies which specifically bind CSG can be injected into patients suspected of having prostate cancer for the purpose of diagnosing or staging of the disease status of the patient. The label used will be selected in accordance with the imaging modality to be used. For example, radioactive labels such as Indium-111, Technetium-99m or Iodine-131 can be used for planar scans or single photon emission computed tomography (SPECT). Positron emitting labels such as Fluorine-19 can be used in positron emission tomography. Paramagnetic ions such as Gadlinium (III) or Manganese (II) can be used in magnetic resonance imaging (MRI). Localization of the label permits determination of the spread of the cancer. The amount of label within an organ or

tissue also allows determination of the presence or absence of cancer in that organ or tissue.

For patients diagnosed with prostate cancer, injection of an antibody which specifically binds CSG can also have a therapeutic benefit. The antibody may exert its therapeutic effect alone. Alternatively, the antibody can be conjugated to a cytotoxic agent such as a drug, toxin or radionuclide to enhance its therapeutic effect. Drug monoclonal antibodies have been described in the art for example by Garnett and Baldwin, Cancer Research 1986 46:2407-2412. The use of toxins conjugated to monoclonal antibodies for the therapy of various cancers has also been described by Pastan et al. Cell 1986 47:641-648. Yttrium-90 labeled monoclonal antibodies have been described for maximization of dose delivered to the tumor while limiting toxicity to normal tissues (Goodwin and Meares Cancer Supplement 1997 80:2675-2680). Other cytotoxic radionuclides including, but not limited to Copper-67, Iodine-131 and Rhenium-186 can also be used for labeling of antibodies against CSG.

Antibodies which can be used in these *in vivo* methods include polyclonal, monoclonal and omniclonal antibodies and antibodies prepared via molecular biology techniques. Antibody fragments and aptamers and single-stranded oligonucleotides such as those derived from an *in vitro* evolution protocol referred to as SELEX and well known to those skilled in the art can also be used.

Small molecules predicted via computer imaging to specifically bind to regions of CSGs can also be designed and synthesized and tested for use in the imaging and treatment of prostate cancer. Further, libraries of molecules can be screened for potential anticancer agents by assessing the ability of the molecule to bind to CSGs identified herein. Molecules identified in the library as being capable of binding to CSG are key candidates for further evaluation for use in the treatment of prostate cancer.

EXAMPLES

The present invention is further described by the following examples. These examples are provided solely to illustrate the invention by reference to specific embodiments. These exemplifications, while illustrating certain aspects of the invention, do not portray the limitations or circumscribe the scope of the disclosed invention.

All examples outlined here were carried out using standard techniques, which are well known and routine to those of skill in the art, except where otherwise described in detail. Routine molecular biology techniques of the following example can be carried out as described in standard laboratory manuals, such as Sambrook et al., MOLECULAR CLONING: A LABORATORY MANUAL, 2nd Ed.; Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1989).

Example 1: Identification of CSGs

Identification of CSGs were carried out by a systematic analysis of data in the LIFESEQ database available from Incyte Pharmaceuticals, Palo Alto, CA, using the data mining Cancer Leads Automatic Search Package (CLASP) developed by diaDexus LLC, Santa Clara, CA.

The CLASP performs the following steps: selection of highly expressed organ specific genes based on the abundance level of the corresponding EST in the targeted organ versus all the other organs; analysis of the expression level of each highly expressed organ specific genes in normal, tumor tissue, disease tissue and tissue libraries associated with tumor or disease; selection of the candidates demonstrating component ESTs were exclusively or more frequently found in tumor libraries. The CLASP allows the identification of highly expressed organ and cancer specific genes. A final manual in depth evaluation is then performed to finalize the CSGs selection.

Clones depicted in the following Table 1 are CSGs useful in diagnosing, monitoring, staging, imaging and treating prostate cancer.

Table 1: CSGs

Clone ID	Pro #	SEQ ID NO:
3424528H1	Pro109	1,2
578349H1	Pro112	3,4
1794013H1	Pro111	5,6
2189835H1	Pro115	7,8
3277219H1	Pro110	9,10
1857415	Pro113	11,12
1810463H1	Pro114	13,14
zr65G11	Pro118	15,16
2626135H1		17
zd46d08		18
1712252H1		19
784583H1		20

Example 2: Relative Quantitation of Gene Expression

Real-Time quantitative PCR with fluorescent Taqman probes is a quantitation detection system utilizing the 5'- 3' nuclease activity of Taq DNA polymerase. The method uses an internal fluorescent oligonucleotide probe (Taqman) labeled with a 5' reporter dye and a downstream, 3' quencher dye. During PCR, the 5'-3' nuclease activity of Taq DNA polymerase releases the reporter, whose fluorescence can then be detected by the laser detector of the Model 7700 Sequence Detection System (PE Applied Biosystems, Foster City, CA, USA).

Amplification of an endogenous control is used to standardize the amount of sample RNA added to the reaction and normalize for Reverse Transcriptase (RT) efficiency. Either cyclophilin, glyceraldehyde-3-phosphate dehydrogenase (GAPDH), ATPase, or 18S ribosomal RNA (rRNA) is used as this endogenous

control. To calculate relative quantitation between all the samples studied, the target RNA levels for one sample were used as the basis for comparative results (calibrator). Quantitation relative to the "calibrator" can be obtained using the standard curve method or the comparative method (User Bulletin #2: ABI PRISM 7700 Sequence Detection System).

The tissue distribution and the level of the target gene were evaluated for every sample in normal and cancer tissues. Total RNA was extracted from normal tissues, cancer tissues, and from cancers and the corresponding matched adjacent tissues. Subsequently, first strand cDNA was prepared with reverse transcriptase and the polymerase chain reaction was done using primers and Taqman probes specific to each target gene. The results were analyzed using the ABI PRISM 7700 Sequence Detector. The absolute numbers are relative levels of expression of the target gene in a particular tissue compared to the calibrator tissue.

Expression of Clone ID 3424528H1 (Pro109):

For the CSG Pro109, real-time quantitative PCR was performed using the following primers:

Forward Primer:

5'- ATCAGAACAAAGAGGCTGTGTC - 3' (SEQ ID NO:21)

Reverse Primer:

5'- ATCTCTAAAGCCCCAACCTTC - 3' (SEQ ID NO:22)

The absolute numbers depicted in Table 2 are relative levels of expression of the CSG referred to as Pro109 in 12 normal different tissues. All the values are compared to normal stomach (calibrator). These RNA samples are commercially available pools, originated by pooling samples of a particular tissue from different individuals.

Table 2: Relative Levels of CSG Pro109 Expression in Pooled Samples

Tissue	NORMAL
Colon	0.02
Endometrium	0.01
Kidney	0.48
Liver	14.83
Ovary	0.08
Pancreas	4.38
Prostate	11.24
Small Intestine	0.42
Spleen	0
Stomach	1
Testis	0.62
Uterus	0.02

The relative levels of expression in Table 2 show that with the exception of liver (14.83), Pro109 mRNA expression is higher (11.24) in prostate compared with all other normal tissues analyzed. Pancreas, with a relative expression level of 4.38, is the only other tissue expressing considerable mRNA for Pro109.

The absolute numbers in Table 2 were obtained analyzing pools of samples of a particular tissue from different individuals. They cannot be compared to the absolute numbers originated from RNA obtained from tissue samples of a single individual in Table 3.

The absolute numbers depicted in Table 3 are relative levels of expression of Pro109 in 28 pairs of matching samples and 4 unmatched samples. All the values are compared to normal stomach (calibrator). A matching pair is formed by mRNA from the cancer sample for a particular tissue and mRNA from the normal adjacent sample for that same tissue from the same individual.

Table 3: Relative Levels of CSG Pro109 Expression in Individual Samples

Sample ID	Tissue	Cancer	Matching Normal Adjacent
Pro34B	Prostate 1	5.98	6.06
Pro65XB	Prostate 2	16.68	3.85
Pro69XB	Prostate 3	20.46	6.82
Pro78XB	Prostate 4	1.39	1.4
Pro101XB	Prostate 5	24.8	9.8
Pro12B	Prostate 6	9.1	0.2
Pro13XB	Prostate 7	0.5	9.7
Pro20XB	Prostate 8	13	12.5
Pro23B	Prostate 9	16.8	3
Ovr10005O	Ovary 1	0.4	
Ovr1028	Ovary 2	1.9	
Ovr18GA	Ovary 3		0.1
Ovr206I	Ovary 4		0.1
Mam12X	Mammary Gland 1	13.5	1.4
Mam47XP	Mammary Gland 2	0.7	0.2
Lng47XQ	Lung 1	2.36	0.03
Lng60XL	Lung 2	7.39	0.2
Lng75XC	Lung 3	0.77	0.27
StoAC44	Stomach 1	0.05	1.19
StoAC93	Stomach 2	0.55	0.8
StoAC99	Stomach 3	0.12	3.04
ColAS43	Colon 1	16.11	0.07
ColAS45	Colon 2	0.11	0.08
ColAS46	Colon 3	4.99	0.4
Liv15XA	Liver 1	8.43	10.97
Liv42X	Liver 2	1.57	20.82

Liv94XA	Liver 3	2.98	9.19
Pan77X	Pancreas 1	36	32
Pan82XP	Pancreas 2	0.09	7.09
Pan92X	Pancreas 3	0.7	0
Pan71XL	Pancreas 4	2.48	0.73
Pan10343	Pancreas 5	46	5.5

0 = Negative

In the analysis of matching samples, the higher levels of expression were in prostate, showing a high degree of tissue specificity for prostate tissue. Of all the samples different than prostate analyzed, only 4 cancer samples (the cancer sample mammary 1 with 13.5, colon 1 with 16.11, liver 1 with 8.43, and lung 2 with 7.39) showed an expression comparable to the mRNA expression in prostate. These results confirmed some degree of tissue specificity as obtained with the panel of normal pooled samples (Table 2).

Furthermore, the level of mRNA expression was compared in cancer samples and the isogenic normal adjacent tissue from the same individual. This comparison provides an indication of specificity for the cancer (e.g. higher levels of mRNA expression in the cancer sample compared to the normal adjacent). Table 3 shows overexpression of Pro109 in 6 out of 9 primary prostate cancer tissues compared with their respective normal adjacents. Thus, overexpression in the cancer tissue was observed in 66.66% of the prostate matching samples tested (total of 9 prostate matching samples).

Altogether, the degree of tissue specificity, plus the mRNA overexpression in 66.66% of the primary prostate matching samples tested is indicative of Pro109 being a diagnostic marker for prostate cancer.

Expression of Clone ID 578349H1 (Pro112):

For the CSG Pro112, real-time quantitative PCR was performed using the following primers:

Forward Primer

5'- TGCCGAAGAGGTTCAGTGC - 3' (SEQ ID NO:23)

Reverse Primer

5'- GCCACAGTGGTACTGTCCAGAT - 3' (SEQ ID NO:24)

The absolute numbers depicted in Table 4 are relative levels of expression of the CSG Pro112 in 12 normal different tissues. All the values are compared to normal thymus (calibrator). These RNA samples are commercially available pools, originated by pooling samples of a particular tissue from different individuals.

Table 4: Relative Levels of CSG Pro112 Expression in Pooled Samples

Tissue	NORMAL
Brain	2.9
Heart	0.1
Kidney	0.2
Liver	0.2
Lung	7.7
Mammary	4.2
Muscle	0.1
Prostate	5.5
Small Intestine	1.8
Testis	1
Thymus	1
Uterus	21

The relative levels of expression in Table 4 show that Pro112 mRNA expression is the 3rd most highly expressed gene (after uterus and mammary) in the pool of normal prostate tissue compared to a total of 12 tissues analyzed. The absolute numbers in Table 4 were obtained analyzing pools of samples of a particular tissue from different individuals. These results demonstrate that Pro112 mRNA expression is specific for prostate thus indicating Pro112 to be a diagnostic marker for prostate disease especially cancer.

Expression of Clone ID 1794013H1 (Pro111):

For the CSG Pro111, real-time quantitative PCR was performed using the following primers:

Forward Primer

5'- GCTGCAAGTTCTCCACATTGA - 3' (SEQ ID NO:25)

Reverse Primer

5'- CAGCCGCAGGTGAAACAC - 3' (SEQ ID NO:26)

The absolute numbers depicted in Table 5 are relative levels of expression of the CSG Pro111 in 12 normal different tissues. All the values are compared to normal testis (calibrator). These RNA samples are commercially available pools, originated by pooling samples of a particular tissue from different individuals.

Table 5: Relative Levels of CSG Pro111 Expression in Pooled Samples

Tissue	NORMAL
Brain	0.04
Heart	0
Kidney	0
Liver	0
Lung	0.05
Mammary	0.14
Muscle	5166.6
Prostate	1483.72
Small Intestine	0.33
Testis	1
Thymus	0.49
Uterus	0.07

The relative levels of expression in Table 5 show that Pro111 mRNA expression is extraordinarily high in the pool of normal prostate (1483.72) compared to all the other tissues analyzed with the exception of muscle (5166.6). These results demonstrate that Pro111 mRNA expression shows specificity for prostate and muscle.

The absolute numbers in Table 5 were obtained analyzing pools of samples of a particular tissue from different

individuals. They cannot be compared to the absolute numbers originated from RNA obtained from tissue samples of a single individual in Table 6.

The absolute numbers depicted in Table 6 are relative levels of expression of Pro111 in 48 pairs of matching and 18 unmatched samples. All the values are compared to normal testis (calibrator). A matching pair is formed by mRNA from the cancer sample for a particular tissue and mRNA from the normal adjacent sample for that same tissue from the same individual.

Table 6: Relative Levels of CSG Pro111 Expression in Individual Samples

Sample ID	Tissue	Cancer	Matching Normal Adjacent
Pro101XB	Prostate 1	8.3	21.8
Pro12B	Prostate 2	2336	133
Pro13XB	Prostate 3	3.4	23
Pro20XB	Prostate 4	21.6	121.5
Pro23B	Prostate 5	19.4	3.7
Pro34B	Prostate 6	15	39
Pro65XB	Prostate 7	8	867
Pro69XB	Prostate 8	56	94
Pro78XB	Prostate 9	24	1515
Pro84XB	Prostate 10	119	15.35
Pro90XB	Prostate 11	8.08	112.2
Pro91XB	Prostate 12	0.88	51.8
ProC215	Prostate 13	0.3	
ProC234	Prostate 14	0.35	
ProC280	Prostate 15	436.5	
Pro109XB	Prostate 16	3.43	265
Pro110	Prostate 17	18.2	8.73

Pro125XB	Prostate 18	0.34	186
Pro326	Prostate 19	1392	110
Pro10R	Prostate 20 (prostatitis)	0.5	
Pro20R	Prostate 21 (prostatitis)	24.1	
Pro258	Prostate 22 (BPH)	4610	
Pro263C	Prostate 23 (BPH)	0	
Pro267A	Prostate 24 (BPH)	1.46	
Pro271A	Prostate 25 (BPH)	0	
Pro460Z	Prostate 26 (BPH)	1.47	
ProC032	Prostate 27 (BPH)	14.4	
Tst39X	Testis 1	0	0
Bld32XK	Bladder 1	0.44	0.41
Bld46XK	Bladder 2	0	0
Bld66X	Bladder 3	0	0
BldTR14	Bladder 4	0	0
Kid106XD	Kidney 1	0	0
Kid107XD	Kidney 2	0	0
Kid109XD	Kidney 3	0	0
Pan10343	Pancreas 1	0	0
Pan71XL	Pancreas 2	0	0
Pan77X	Pancreas 3	0	0
Liv15XA	Liver 1	0	0
Liv42X	Liver 2	0	0
ClnAS43	Colon 1	0	0
ClnAS45	Colon 2	0	0
ClnAS46	Colon 3	0	0
ClnAS67	Colon 4	0	0
ClnAC19	Colon 5	0	0
ClnAS12	Colon 6	0	0

SmI21XA	Small Intestine 1	0	0
SmIH89	Small Intestine 2	0	0
Lng47XQ	Lung 1	0.7	0
Lng60XL	Lung 2	0	0
Lng75XC	Lung 3	0	0
Lng90X	Lung 4	0	0
Mam12X	Mammary Gland 1	0	1.4
Mam59X	Mammary Gland 2	0.2	0
MamA06X	Mammary Gland 3	0	0
MamS127	Mammary Gland 4	0	0
Mam162X	Mammary Gland 5	0	0
Mam42DN	Mammary Gland 6	0	0
Ovr103X	Ovary 1	0.14	0
Ovr1005O	Ovary 2	0.2	
Ovr1028	Ovary 3	0	
Ovr1040O	Ovary 4	0.2	
Ovr18GA	Ovary 5		0
Ovr206I	Ovary 6		0
Ovr20GA	Ovary 7		0.2
Ovr25GA	Ovary 8		0

0= Negative

In the analysis of matching samples, the higher levels of expression were in prostate showing a high degree of tissue specificity for prostate. These results confirm the tissue specificity results obtained with normal pooled samples (Table 5).

Furthermore, the level of mRNA expression in cancer samples and the isogenic normal adjacent tissue from the same individual were compared. This comparison provides an indication of specificity for cancer (e.g. higher levels of mRNA expression in the cancer sample compared to the normal adjacent). Table 6 shows overexpression of Pro111 in 5 out

of 16 primary prostate cancer samples compared with their respective normal adjacent (prostate samples 2, 5, 10, 17, and 19). Similar expression levels were observed in 3 unmatched prostate cancers (prostate samples 13, 14, 15), 2 prostatitis (prostate samples 20, 21), and 6 benign prostatic hyperplasia samples (prostate samples 22 through 27). Thus, there is overexpression in the cancer tissue of 31.25% of the prostate matching samples tested (total of 16 prostate matching samples).

Altogether, the high level of tissue specificity, plus the mRNA overexpression in 31.25% of the prostate matching samples tested are indicative of Pro111 being a diagnostic marker for prostate cancer.

Expression of Clone ID 2189835H1 (Pro115):

For the CSG Pro115, real-time quantitative PCR was performed using the following primers:

Forward Primer

5'- TGGCTTTGAACTCAGGGTCA - 3' (SEQ ID NO:27)

Reverse Primer

5'- CGGATGCACCTCGTAGACAG - 3' (SEQ ID NO:28)

The absolute numbers depicted in Table 7 are relative levels of expression of the CSG Pro115 in 12 normal different tissues. All the values are compared to normal thymus (calibrator). These RNA samples are commercially available pools, originated by pooling samples of a particular tissue from different individuals.

Table 7: Relative Levels of CSG Pro115 Expression in Pooled Samples

Tissue	NORMAL
Brain	0.016
Heart	0.002
Kidney	8.08
Liver	2.20
Lung	112.99

Mammary	29.45
Muscle	0.05
Prostate	337.79
Small Intestine	7.54
Testis	1.48
Thymus	1
Uterus	1.4

The relative levels of expression in Table 7 show that Pro115 mRNA expression is higher (337.79) in prostate compared with all the other normal tissues analyzed. Lung, with a relative expression level of 112.99, and mammary (29.446) are the other tissues expressing moderate levels of mRNA for Pro115. These results establish Pro115 mRNA expression to be highly specific for prostate.

The absolute numbers in Table 7 were obtained analyzing pools of samples of a particular tissue from different individuals. They cannot be compared to the absolute numbers originated from RNA obtained from tissue samples of a single individual in Table 8.

The absolute numbers depicted in Table 8 are relative levels of expression of Pro115 in 17 pairs of matching and 21 unmatched samples. All the values are compared to normal thymus (calibrator). A matching pair is formed by mRNA from the cancer sample for a particular tissue and mRNA from the normal adjacent sample for that same tissue from the same individual.

Table 8: Relative Levels of CSG Pro115 Expression in Individual Samples

Sample ID	**Tissue**	**Cancer**	**Matching Normal Adjacent**
Pro12B	Prostate 1	1475.9	190.3
ProC234	Prostate 2	169.61	
Pro109XB	Prostate 3		639.53
Pro101XB	Prostate 4	1985.2	2882.9

Pro13XB	Prostate 5	34.9	13.9
Pro215	Prostate 6	525.59	
Pro125XB	Prostate 7		556.05
Pro23B	Prostate 8	1891.4	1118.6
ProC280	Prostate 9	454.3	
Pro20XB	Prostate 10	1332.6	
Pro34B	Prostate 11		362.91
Pro65XB	Prostate 12		135.06
Pro69XB	Prostate 13		179.67
Pro10R	Prostate 14 (prostatitis)	143.82	
Pro20R	Prostate 15 (prostatitis)	397.79	
Pro258	Prostate 16 (BPH)	216.6	
Pro263C	Prostate 17 (BPH)	601.25	
Pro267A	Prostate 18 (BPH)	200.28	
Pro271A	Prostate 19 (BPH)	111.43	
Pro460Z	Prostate 20 (BPH)	53.84	
ProC032	Prostate 21 (BPH)	56.94	
SmI21XA	Small Intestine 1	28.8	29.9
SmIH89	Small Intestine 2	70.8	348.5
ClnAC19	Colon 1	22.73	446.47
ClnAS12	Colon 2	116.97	493.18
Kid106XD	Kidney 1	86.13	41.14
Kid107XD	Kidney 2	0.26	35.14
Lng47XQ	Lung 1	5.13	20.98
Lng60XL	Lung 2	13.93	114.78
Lng75XC	Lung 3	16.47	53.79
Mam12X	Mammary Gland 1	6.25	10.75
Mam162X	Mammary Gland 2	1.84	2.54
Mam42DN	Mammary Gland 3	23.08	35.51

Ovr10050	Ovary 1	0.9	
Ovr1028	Ovary 2	261.4	
Ovr103X	Ovary 3	7	0.1
Ovr20GA	Ovary 4		0
Ovr25GA	Ovary 5		0

0 = Negative

Higher levels of expression were seen in prostate, showing a high degree of tissue specificity for prostate tissue. Of all the analyzed samples different from prostate, only two cancer samples (colon 2 with 116.97 and ovary 2 with 261.4), and 5 normal adjacent tissue samples (small intestine 2, colon 1, colon 2, kidney 1, and lung 2), showed an expression comparable to the mRNA expression in prostate. These results confirmed the tissue specificity results obtained with the panel of normal pooled samples (Table 7).

Furthermore, the levels of mRNA expression in cancer samples and the isogenic normal adjacent tissue from the same individual were compared. This comparison provides an indication of specificity for the cancer (e.g. higher levels of mRNA expression in the cancer sample compared to the normal adjacent). Table 8 shows higher expression of Pro115 in 3 out of 4 matched prostate cancer tissues (prostate samples 1, 5 & 8).

Altogether, the high level of tissue specificity, plus the higher expression in 75% of the prostate matching samples tested, are indicative of Pro115 being a diagnostic marker for prostate cancer.

Expression of Clone ID 3277219H1 (Pro110):

For the CSG Pro110, real-time quantitative PCR was performed using the following primers:

Forward Primer

5'- CGGCAACCTGGTAGTGAGTG - 3' (SEQ ID NO:29)

Reverse Primer

5'- CGCAGCTCCTTGTAAACTTCAG - 3' (SEQ ID NO:30)

The absolute numbers depicted in Table 9 are relative levels of expression of the CSG Pro110 in 12 normal different tissues. All the values are compared to normal small intestine (calibrator). These RNA samples are commercially available pools, originated by pooling samples of a particular tissue from different individuals.

Table 9: Relative Levels of CSG Pro110 Expression in Pooled Samples

Tissue	NORMAL
Brain	6.61
Heart	0.7
Kidney	0.74
Liver	7.94
Lung	11.88
Mammary	22.78
Muscle	6.77
Prostate	3.01
Small Intestine	1
Testis	2.58
Thymus	13.74
Uterus	2.61

The relative levels of expression in Table 9 show that Pro110 mRNA expression is not as high in normal prostate (3.01) compared with all the other normal tissues analyzed.

The absolute numbers in Table 9 were obtained analyzing pools of samples of a particular tissue from different individuals. They cannot be compared to the absolute numbers originated from RNA obtained from tissue samples of a single individual in Table 10.

The absolute numbers depicted in Table 10 are relative levels of expression of Pro110 in 33 pairs of matching samples. All the values are compared to normal small intestine (calibrator). A matching pair is formed by mRNA from the cancer sample for a particular tissue and mRNA from

the normal adjacent sample for that same tissue from the same individual.

Table 10: Relative Levels of CSG Pro110 Expression in Individual Samples

Sample ID	Tissue	Cancer	Matching Normal Adjacent
Pro12B	Prostate 1	11.8	0.3
Pro78XB	Prostate 2	14.3	6.3
Pro101XB	Prostate 3	33.2	10.7
Pro13XB	Prostate 4	0.3	0.4
Pro23XB	Prostate 5	25.5	14.4
Pro20XB	Prostate 6	43.3	4
Pro34XB	Prostate 7	31.8	18.7
Pro65XB	Prostate 8	26.9	3.4
Pro69XB	Prostate 9	12.5	7
Lng75XC	Lung 1	1.9	3
Lng90X	Lung 2	5.5	0.5
LngAC11	Lung 3	9.3	9.7
LngAC32	Lung 4	11.2	2.2
Lng47XQ	Lung 5	11.3	0.3
Lng60XL	Lung 6	29.1	6.8
Mam12B	Mammary Gland 1	19.8	0
Mam603X	Mammary Gland 2	13.7	0
Mam82XI	Mammary Gland 3	73.5	0
MamA04	Mammary Gland 4	0	24.6
MamB011X	Mammary Gland 5	17.4	2
MamC012	Mammary Gland 6	0	12.8
MamC034	Mammary Gland 7	0	61
Mam12X	Mammary Gland 8	14	2.2
Mam59X	Mammary Gland 9	33	2.2

MamA06X	Mammary Gland 10	16.4	0.8
Liv15XA	Liver 1	4.7	0.6
Liv42X	Liver 2	7.5	2.6
Liv94XA	Liver 3	0.4	1.4
ClnAS43	Colon 1	52.9	1.4
ClnAS45	Colon 2	2.1	0.8
ClnAS46	Colon 3	39.8	3.7
SmI21X	Small Intestine 1	0.9	0.1
SmIH89	Small Intestine 2	5.8	0.9

0 = Negative

The levels of mRNA expression in cancer samples and the isogenic normal adjacent tissue from the same individual were compared. This comparison provides an indication of specificity for the cancer (e.g. higher levels of mRNA expression in the cancer sample compared to the normal adjacent). Table 10 shows overexpression of Pro110 in 8 of the 9 primary prostate cancer tissues compared with their respective normal adjacent (except prostate 4). Thus, there was overexpression in 88.88% of the cancer prostate tissue as compared to the prostate matching samples tested (total of 9 prostate matching samples).

Although not tissue specific, Pro110 mRNA expression is upregulated in prostate cancer tissues. The mRNA overexpression in 88.88% of the primary prostate matching cancer samples tested is indicative of Pro110 being a diagnostic marker for prostate cancer. Pro110 also showed overexpression in several other cancers tested including small intestine, colon, liver, mammary and lung (see Table 10). Accordingly Pro110 may be a diagnostic marker for other types of cancer as well.

Expression of Clone ID 1857415; Gene ID 346880 (Pro113):

For the CSG Pro113, real-time quantitative PCR was performed using the following primers:

Forward Primer

5'- CGGGAACCTACCAGCCTATG - 3' (SEQ ID NO:31)

Reverse Primer

5'- CAGGCAACAGGGAGTCATGT - 3' (SEQ ID NO:32)

The absolute numbers depicted in Table 11 are relative levels of expression of the CSG Pro113 in 12 normal different tissues. All the values are compared to normal thymus (calibrator). These RNA samples are commercially available pools, originated by pooling samples of a particular tissue from different individuals.

Table 11: Relative Levels of CSG Pro113 Expression in Pooled Samples

Tissue	NORMAL
Brain	0.03
Heart	0
Kidney	0.01
Liver	0
Lung	0
Mammary Gland	0
Muscle	0.04
Prostate	489.44
Small Intestine	0.02
Testis	0.35
Thymus	1
Uterus	0.13

The relative levels of expression in Table 11 show that Pro113 mRNA expression is higher (489.44) in prostate compared with all the other normal tissues analyzed. Testis, with a relative expression level of 0.35, uterus (0.13), thymus (1.0), kidney (0.01) and brain (0.03) were among the other tissues expressing lower mRNA levels for Pro113. These results establish that Pro113 mRNA expression is highly specific for prostate.

The absolute numbers in Table 11 were obtained analyzing pools of samples of a particular tissue from different individuals. They cannot be compared to the absolute numbers originated from RNA obtained from tissue samples of a single individual in Table 12.

The absolute numbers depicted in Table 12 are relative levels of expression of Pro113 in 78 pairs of matching and 25 unmatched tissue samples. All the values are compared to normal thymus (calibrator). A matching pair is formed by mRNA from the cancer sample for a particular tissue and mRNA from the normal adjacent sample for that same tissue from the same individual. In cancers (for example, ovary) where it was not possible to obtain normal adjacent samples from the same individual, samples from a different normal individual were analyzed.

Table 12: Relative Levels of CSG Pro113 Expression in Individual Samples

Sample ID	Tissue	Cancer	Matched or Unmatched Normal Adjacent
Pro780B/781B	Prostate 1	375.58	446.29
Pro1291B/1292B	Prostate 2	1060	31
Pro139B96/140B96	Prostate 3	41	32
Pro209B96/210B96	Prostate 4	505	255
Pro1256B/1257B	Prostate 5	165.79	141.63
Pro1293B/1294B	Prostate 6	1613.7	874.61
Pro694B/695B	Prostate 7	458.6	142.21
Pro1012B/1013B	Prostate 8	1520	864
Pro1222B/1223B	Prostate 9	939	530
Pro845B/846B	Prostate 10	1552.4	374.6
Pro1094B/1095B	Prostate 11	278.37	135.89
Pro650B/651B	Prostate 12	532.81	640.85

Pro902B/903B	Prostate 13	609.05	415.86
Pro916B/917B	Prostate 14	699.42	401.24
Pro9821110A/110B	Prostate 15	156	487.8
ProS9821326A/26B	Prostate 16	744.4	472.8
Pro9407c215	Prostate 17	1389.2	
Pro9407c234	Prostate 18	305.5	
Pro9407c280A	Prostate 19	894.5	
Pro9409C010R	Prostate 20 (prostatitis)	269.7	
Pro9404C120R	Prostate 21 (prostatitis)	299.2	
Pro1000258	Prostate 22 (BPH)	149.6	
Pro4001263C	Prostate 23 (BPH)	576	
Pro4001267A	Prostate 24 (BPH)	132.1	
Pro9411C032	Prostate 25 (BPH)	118.2	
Pro4001460Z	Prostate 26 (BPH)	276.3	
Pro4001271A	Prostate 27 (BPH)	58.7	
Kid1064D/65D	Kidney 1	0	0.1
Kid1079D/1080D	Kidney 2	0.3	0.02
Kid1097D/1098D	Kidney 3	35.14	0.32
Kid1024D/1025D	Kidney 4	1.31	0
Kid1183D/1184D	Kidney 5	24.79	0
Kid1242D/1243D	Kidney 6	0	0
Bld469K	Bladder 1		2.88
Bld467K/468K	Bladder 2	2.65	
Bld327K/328K	Bladder 3	0	4.05
Bld470K	Bladder 4		1.64
Bld665T/664T	Bladder 5	0.21	1.99

Bld1496K/1497K	Bladder 6	13.55	1.14
Bld1721K/1722K	Bladder 7	120.16	1.34
Tst239X/240X	Testis 1	31.5	0.73
TstS9820647A/47B	Testis 2	15.7	0
TstS9820663A/663B	Testis 3	72	1.4
SknS9821248A/248B	Skin 1	1.8	0.5
SknS99448A/448B	Skin 2	251.6	0
Skn99816A/816B	Skin 3	33	0.7
Sto4004864A4/B4	Stomach 1	14.12	0
Sto4004509A3/B1	Stomach 2	40.74	39
SmI9807A212A/213A	Small Intestine 1	0.1	0
SmI9802H008/H009	Small Intestine 2	5.8	0.1
Cln9608B012/B011	Colon 1	4.5	0
Cln9709c074ra/073ra	Colon 2	65.8	3.1
Cln4004709A1/709B1	Colon 3	1.1	0.9
Cln9405C199/C200	Colon 4	34.76	0.73
Cln9707c004gb/006ga	Colon 5	90.26	0.96
Cln96-09-B004/B003	Colon 6	17.9	20.64
Cln9612B006/B005	Colon 7	17.56	0.3
Cln9705F002D/F001C	Colon 8	21.39	0
ClnCXGA	Colon 9	429.14	142.69
Pan10343a	Pancreas 1	0	0
Pan776P/777P	Pancreas 2	0	0.15
Pan921O/922O	Pancreas 3	7.36	0
Pan714L/715L	Pancreas 4	13.57	0.11
Pan824P/825P	Pancreas 5	0	0
Lng476Q/477Q	Lung 1	0	0
Lng605L/606L	Lung 2	0	0.1
Lng11145B/11145C	Lung 3	85.9	0

Lng0008632A/32B	Lung 4	23.85	0
Lng750C/751C	Lung 5	0.32	0.25
Lng8890A/8890B	Lung 6	10.63	0
Lng8926A/8926B	Lung 7	15.37	0
Lng0010239A/39B	Lung 8	26.17	0
Lng9502C109R/110R	Lung 9	0.68	0
LngS9821944a/44b	Lung 10	0	0
Mam00042D01/42N01	Mammary Gland 1	8.5	0
Mam59XC	Mammary Gland 2	61.07	0
Mam9706A066G/67C	Mammary Gland 3	4.84	0
Mam14153a1C	Mammary Gland 4	9.72	6.99
Mam1620F/1621F	Mammary Gland 5	0.91	0
Mam00014D05	Mammary Gland 6	2.45	0
End10479B/D	Endometrium 1	133.43	1.12
End9705A125A/126A	Endometrium 2	0	0.39
End9704C281A/282A	Endometrium 3	23.5	1.56
End680o97/681o97	Endometrium 4	88.89	79.02
Utr1359O/1358O	Uterus 1	0.2	0
Utr850U/851U	Uterus 2	0	0
Utr1417O/1418O	Uterus 3	14	0.4
Utr233U96/234U96	Uterus 4	8.65	4.64
CvxVNM00052D01/52N01	Cervix 1	0.82	77.15
CvxVNM00083D01/83N01	Cervix 2	0.78	221.48
CvxND00023D01/23N01	Cervix 3	3.25	15.22
Ovr1037O/1038O	Ovary 1	0.1	0
Ovr1005O	Ovary 2	18.96	
Ovr1028	Ovary 3	0	
Ovr14638A1C	Ovary 4	3.2	
Ovr14603A1D	Ovary 5	882.3	
Ovr773O	Ovary 6	0	

Ovr9702C018GA	Ovary 7		0.15
Ovr206I	Ovary 8		0
Ovr9702C020GA	Ovary 9		0
Ovr9702C025GA	Ovary 10		0
Ovr9701C035GA	Ovary 11		0.07
Ovr9701C050GB	Ovary 12		0.58

0 = Negative

In the analysis of matching samples, the higher levels of expression were in prostate, showing a high degree of tissue specificity for prostate tissue. In addition to the higher expression levels in prostate cancer samples, Pro113 expression was found to be either induced (where not expressed in normal adjacent tissues) or somewhat upregulated in several other cancers. However, the relative expression and the fold increase in prostate cancer samples far exceeds that in other cancer tissues and is highly significant.

Furthermore, the levels of mRNA expression in cancer samples and the isogenic normal adjacent tissue from the same individual were compared. This comparison provides an indication of specificity for the cancer (e.g. higher levels of mRNA expression in the cancer sample compared to the normal adjacent). Table 12 shows overexpression of Pro113 in 13 out of 16 primary prostate cancer tissues compared with their respective normal adjacent (prostate samples 2, 3, 4, 5, 6 7, 8, 9, 10, 11, 13, 14, 16). Thus, there was overexpression in the cancer tissue for 81.25% of the prostate matching samples tested. The median for the level of expression in prostate cancer tissue samples is 609, whereas the median for all other cancers is only 7.93, with the exception of one colon sample, colon 9, whose expression was similar to that found in prostate cancer tissues.

Altogether, the high level of tissue specificity, plus the mRNA overexpression in 81.25% of the primary prostate matching samples tested are indicative of Pro113 being a

diagnostic marker for prostate cancer. Expression was also found to be higher in other cancer tissues compared with their respective normal adjacent tissues (kidney, bladder, testis, skin, stomach, small intestine, colon, pancreas, lung, mammary, endometrium, uterus, and ovary) thus indicating Pro113 to be a pan cancer marker.

Expression of Clone ID 1810463H1 (Pro114):

For the CSG Pro114, real-time quantitative PCR was performed using the following primers:

Forward Primer

5'- TGGGCATCTGGGTGTCAA - 3' (SEQ ID NO:33)

Reverse Primer

5'- CGGCTGCGATGAGGAAGTA - 3' (SEQ ID NO:34)

The absolute numbers depicted in Table 13 are relative levels of expression of the CSG Pro114 in 12 normal different tissues. All the values are compared to normal muscle (calibrator). These RNA samples are commercially available pools, originated by pooling samples of a particular tissue from different individuals.

Table 13: Relative Levels of CSG Pro114 Expression in Pooled Samples

Tissue	NORMAL
Brain	9.7
Heart	0.7
Kidney	414.4
Liver	4
Lung	882.2
Mammary	44
Muscle	1
Prostate	1951
Small Intestine	22
Testis	367.1
Thymus	25.8
Uterus	139.6

The relative levels of expression in Table 13 show that Pro114 mRNA expression is higher (1951) in prostate compared with all the other normal tissues analyzed. Lung, with a relative

expression level of 882.2, kidney 414.4, testis 367.1 and uterus 139.6, are the other tissues expressing higher levels of mRNA for Pro114. These results establish Pro114 mRNA expression to be more specific for prostate than other tissues examined.

The high level of tissue specificity is indicative of Pro114 being a diagnostic marker for diseases of the prostate, especially cancer.

Expression of Clone ID zr65g11 (Pro118):

For the CSG Pro118, real-time quantitative PCR was performed using the following primers:

Forward Primer

5'- GCCCATCTCCTGCTTCTTTAGT - 3' (SEQ ID NO:35)

Reverse Primer

5'- CGTGGAGATGGCTCTGATGTA - 3' (SEQ ID NO:36)

The absolute numbers depicted in Table 14 are relative levels of expression of the CSG Pro118 in 12 normal different tissues. All the values are compared to normal kidney (calibrator). These RNA samples are commercially available pools, originated by pooling samples of a particular tissue from different individuals.

Table 14: Relative Levels of CSG Pro118 Expression in Pooled Samples

Tissue	NORMAL
Colon	0.87
Endometrium	19282
Kidney	1
Liver	0
Ovary	86.22
Pancreas	0
Prostate	962.1
Small Intestine	0
Spleen	0.75
Stomach	0.54
Testis	343.7
Uterus	1064

The relative levels of expression in Table 14 show that Pro118 mRNA expression is the 3rd highest in prostate (962.1) next to endometrium (19282) and uterus (1064), which are female-specific tissues. Testis, with a relative expression level of 343.7 is the only other male tissue expressing moderate levels of mRNA for Pro118. These results establish Pro118 mRNA expression to be highly specific for reproductive tissues including the prostate.

The absolute numbers in Table 14 were obtained analyzing pools of samples of a particular tissue from different individuals. They cannot be compared to the absolute numbers originated from RNA obtained from tissue samples of a single individual in Table 15.

The absolute numbers depicted in Table 15 are relative levels of expression of Pro118 in 59 pairs of matching and 21 unmatched samples. All the values are compared to normal kidney (calibrator). A matching pair is formed by mRNA from the cancer sample for a particular tissue and mRNA from the normal adjacent sample for that same tissue from the same individual.

Table 15: Relative Levels of CSG Pro118 Expression in Individual Samples

Sample ID	Tissue	Cancer	Matching Normal Adjacent
Pro12B	Prostate 1	41700.7	22242.83
ProC234	Prostate 2	40087	
Pro78XB	Prostate 3	4075.6	7066.7
Pro109XB	Prostate 4	334.4	777.2
Pro84XB	Prostate 5	11684	58290
Pro101XB	Prostate 6	21474.13	100720.8
Pro91X	Prostate 7	14849	33717
Pro13XB	Prostate 8	202.57	146.91

ProC215	Prostate 9	73243	
Pro125XB	Prostate 10	629.6	521.4
Pro23B	Prostate 11	157532.6	110654.4
Pro90XB	Prostate 12	2317	64134
ProC280	Prostate 13	42020	
Pro20XB	Prostate 14	2909.31	
Pro34B	Prostate 15	29610	23264
Pro110	Prostate 16	13354	30991
Pro65XB	Prostate 17	10126	11270
Pro69XB	Prostate 18		2671.42
Pro326	Prostate 19	9962.3	19231
Pro10R	Prostate 20 (prostatitis)	27355	
Pro20R	Prostate 21 (prostatitis)	21081	
Pro258	Prostate 22 (BPH)	79916.32	
Pro263C	Prostate 23 (BPH)	108924.5	
Pro267A	Prostate 24 (BPH)	92910.22	
Pro271A	Prostate 25 (BPH)	57004.4	
Pro460Z	Prostate 26 (BPH)	57449.23	
ProC032	Prostate 27 (BPH)	45781.44	
Kid106XD	Kidney 1	3.08	217.36
Kid107XD	Kidney 2	0	38.36
Kid109XD	Kidney 3	0	123.5
Kid10XD	Kidney 4	17.69	67.8
Kid11XD	Kidney 5	16.74	360.8
Kid124D	Kidney 6	0	167.4
Bld32XK	Bladder 1	0	0
Bld47K	Bladder 2		36.38
Bld66X	Bladder 3	0	4.52
BldTR14	Bladder 4	0	12.17

BldTR17	Bladder 5	0	0
Bld46XK	Bladder 6	16.5	0
Tst39X	Testis 1	116.6	24.35
Tst647T	Testis 2	856.16	43.5
StoAC44	Stomach 1	0	0
StoAC93	Stomach 2	0	0
SmI21XA	Small Intestine 1	68.45	0
SmIH89	Small Intestine 2	0	0
ClnAC19	Colon 1	149	21.33
ClnAS12	Colon 2	0	0
ClnB34	Colon 3	0	0
ClnB56	Colon 4	13.04	5.22
ClnAS43	Colon 5	0	0
Lng47XQ	Lung 1	0	0
Lng60XL	Lung 2	0	0
Lng75XC	Lung 3	0	3.38
Lng90X	Lung 4	0	0
LngBR26	Lung 5	0	26.82
Pan10343	Pancreas 1	50.47	0
Pan77X	Pancreas 2	281.1	0
Pan92X	Pancreas 3	18.41	0
Pan71XL	Pancreas 4	0	0
Pan82XP	Pancreas 5	0	0
PanC044	Pancreas 6	0	0
Mam12X	Mammary Gland 1	0	0
Mam162X	Mammary Gland 2	0	0
Mam42DN	Mammary Gland 3	0	0
MamS127	Mammary Gland 4	12.58	0
Mam14DN	Mammary Gland 5	0	0
End28XA	Endometrium 1	331.9	1824

End3AX	Endometrium 2	27825	65839
End4XA	Endometrium 3	10.3	15935
Utr141O	Uterus 1	18885	18116
Utr23XU	Uterus 2	3358	7674
CvxKS52	Cervix 1	0	0
CvxKS83	Cervix 2	0	0
Ovr1005O	Ovary 1	72.86	
Ovr1028	Ovary 2	0	
Ovr638A	Ovary 3	0	
Ovr63A	Ovary 4	90.88	
Ovr773O	Ovary 5	1.21	
Ovr1040O	Ovary 6	5.08	
Ovr105O	Ovary 7	0	
Ovr1118	Ovary 8	7.41	
Ovr103X	Ovary 9		32.78
Ovr20GA	Ovary 10		0
Ovr25GA	Ovary 11		1173.83
Ovr35GA	Ovary 12		313.4
Ovr50GB	Ovary 13		823.1
Ovr18GA	Ovary 14		40.6
Ovr206I	Ovary 15		1264
Ovr230A	Ovary 16		1285

0 = Negative

In the analysis of matching samples, the higher levels of expression were in prostate, endometrium, testis, and ovary showing a high degree of tissue specificity for reproductive tissues. These results confirmed the tissue specificity results obtained with the panel of normal pooled samples (Table 14).

Furthermore, the levels of mRNA expression in cancer samples and the isogenic normal adjacent tissue from the same individual were compared. This comparison provides an

indication of specificity for the cancer (e.g. higher levels of mRNA expression in the cancer sample compared to the normal adjacent). Table 15 shows overexpression of Pro118 in 5 out of 14 primary prostate cancer tissues (prostate samples 1, 8, 10, 11, 15) compared with their respective normal adjacent. Thus, there was overexpression in the cancer tissue for 35.71% of the prostate matching samples tested (total of 14 prostate matching samples). Expression of Pro118 was similarly higher in 3 unmatched cancer tissues (prostate samples 9, 13, 14), 2 prostatitis (prostate samples 20, 21), and 6 benign hyperplasia tissues (prostate samples 22 through 27).

Altogether, the high level of tissue specificity, plus the mRNA overexpression in 35.71% of the primary prostate matching samples tested are indicative of Pro118 being a diagnostic marker for prostate cancer.

What is claimed is:

1. A method for diagnosing the presence of prostate cancer in a patient comprising:

(a) determining levels of CSG in cells, tissues or bodily fluids in a patient; and

(b) comparing the determined levels of CSG with levels of CSG in cells, tissues or bodily fluids from a normal human control, wherein a change in determined levels of CSG in said patient versus normal human control is associated with the presence of prostate cancer.

2. A method of diagnosing metastases of prostate cancer in a patient comprising:

(a) identifying a patient having prostate cancer that is not known to have metastasized;

(b) determining CSG levels in a sample of cells, tissues, or bodily fluid from said patient; and

(c) comparing the determined CSG levels with levels of CSG in cells, tissue, or bodily fluid of a normal human control, wherein an increase in determined CSG levels in the patient versus the normal human control is associated with a cancer which has metastasized.

3. A method of staging prostate cancer in a patient having prostate cancer comprising:

(a) identifying a patient having prostate cancer;

(b) determining CSG levels in a sample of cells, tissue, or bodily fluid from said patient; and

(c) comparing determined CSG levels with levels of CSG in cells, tissues, or bodily fluid of a normal human control, wherein an increase in determined CSG levels in said patient versus the normal human control is associated with a cancer which is progressing and a decrease in the determined CSG levels is associated with a cancer which is regressing or in remission.

4. A method of monitoring prostate cancer in a patient for the onset of metastasis comprising:

(a) identifying a patient having prostate cancer that is not known to have metastasized;

(b) periodically determining levels of CSG in samples of cells, tissues, or bodily fluid from said patient; and

(c) comparing the periodically determined CSG levels with levels of CSG in cells, tissues, or bodily fluid of a normal human control, wherein an increase in any one of the periodically determined CSG levels in the patient versus the normal human control is associated with a cancer which has metastasized.

5. A method of monitoring a change in stage of prostate cancer in a patient comprising:

(a) identifying a patient having prostate cancer;

(b) periodically determining levels of CSG in cells, tissues, or bodily fluid from said patient; and

(c) comparing the periodically determined CSG levels with levels of CSG in cells, tissues, or bodily fluid of a normal human control, wherein an increase in any one of the periodically determined CSG levels in the patient versus the normal human control is associated with a cancer which is progressing in stage and a decrease is associated with a cancer which is regressing in stage or in remission.

6. A method of identifying potential therapeutic agents for use in imaging and treating prostate cancer comprising screening molecules for an ability to bind to CSG wherein the ability of a molecule to bind to CSG is indicative of the molecule being useful in imaging and treating prostate cancer.

7. The method of claim 1, 2, 3, 4, 5 or 6 wherein the CSG comprises SEQ ID NO:1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12,

13, 14, 15, 16, 17, 18, 19 or 20 or a polypeptide encoded thereby.

8. An antibody which specifically binds CSG.

9. A method of imaging prostate cancer in a patient comprising administering to the patient an antibody of claim 8.

10. The method of claim 9 wherein said antibody is labeled with paramagnetic ions or a radioisotope.

11. A method of treating prostate cancer in a patient comprising administering to the patient an antibody of claim 7.

12. The method of claim 11 wherein the antibody is conjugated to a cytotoxic agent.

SEQUENCE LISTING

<110> Salceda, Susana
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diaDexus, LLC

<120> Method of Diagnosing, Monitoring, Staging, Imaging and
Treating Prostate Cancer

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/24331

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/130.1, 141.1, 155.1, 183.1; 435/6, 7.1, 7.23, 7.9, 91.2; 436/501, 504, 505, 547; 514/44; 536/23.5

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Medline, Biosis, Embase, Cancerlit, Scisearch, WPIDS, USPATFULL
search terms: CSG, cancer specific gene, cancer, diagnosis

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Database SCISEARCH, Accession Number 307617, OLSSON et al. Reverse transcriptase-polymerase chain reaction assays for prostate cancer. Urologic Clinics of North America. May 1997, Vol. 24 No. 2, pages 367-&.	1-6
Y	CHO-CHUNG et al. Antisense Oligonucleotides for the treatment of cancer. Current Opinion in Therapeutic Patents. 1993, Vol. 3, No. 12, pages 1737-1750, see entire document.	1-6
A,E	BUSSEMAKERS et al. DD3: A new prostate-specific gene, highly overexpressed in prostate cancer. Cancer Research. 01 December 1999, Vol. 59, No. 23, pages 5975-5979.	1-7

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search: 10 FEBRUARY 2000

Date of mailing of the international search report: 07 MAR 2000

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/24331

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (7):

A61K 39/395, 48/00; C12P 19/34; C12Q 1/68; G01N 33/53, 33/574, 33/546, 33/567

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

424/130.1, 141.1, 155.1, 183.1; 435/6, 7.1, 7.23, 7.9, 91.2; 436/501, 504, 505, 547; 514/44; 536/23.5